WOMEN'S HEALTH: HORMONES, EMOTIONS, AND BEHAVIOR

REGINA C. CASPER
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine

CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge, CB2 1RP, United Kingdom

CAMBRIDGE UNIVERSITY PRESS
The Edinburgh Building, Cambridge CB2 2RU, United Kingdom
40 West 20th Street, New York, NY 10011-4211, USA
10 Stamford Road, Oakleigh, Melbourne 3166, Australia

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First published 1998

Printed in the United States of America

Typeset in Garamond

Library of Congress Cataloging-in-Publication Data

Women's health : hormones, emotions, and behavior / edited by
Regina C. Casper.
p. cm. – (Cambridge studies in medicine)
Includes bibliographical references.
ISBN 0-521-56341-0 (hardcover)
1. Women – Mental health. 2. Women – Health and hygiene.
3. Psychoneuroendocrinology. I. Casper, Regina C. II. Series.
RC451.4.W6W659 1997
616.89'0082 – DC21 97-3022
CIP

*A catalog record for this book is available from
the British Library*

ISBN 0-521-56341-0 hardback

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CHAPTER ONE

GROWING UP FEMALE

REGINA C. CASPER

Population statistics consistently record more male than female human births (Babb, 1995), the outcome of a significantly higher conception rate for males (McMillen, 1979). Such sex ratio bias occurs in several species, where research is now examining environmental and physiologic conditions as well as maternal effects that influence the sex ratio at conception and at birth (Bacon and McClintock, 1994). This higher birth rate notwithstanding, beginning at birth and throughout life, male mortality tends to be significantly higher. In the first year of life, 25 percent more male than female infants die, and in adult life the male:female mortality ratio exceeds 2:1 (U.S. Bureau of the Census, 1990).

This phenomenon of women outranking men in survival is relatively new. Until the last century, before the discovery of antisepsis and antibiotics, many young women died in their child beds as a result of birth complications, hemorrhages, and postpartum infections. In 1868, maternal mortality rates were 84.4:1,000 births as opposed to 5:1,000 births in 1986 (O'Dowd and Philipp, 1994). Furthermore, some illnesses are unique to women. Medical complications and pathology associated with the female reproductive system, with pregnancy, and with child rearing confer increased risks of physical and psychological morbidity.

This first chapter presents a necessarily abbreviated account of normal female somatic and psychological development as an introduction to the material in the following chapters, which cover disorders that are known to affect women uniquely or disproportionately.

Postnatal growth

Sexual differentiation and hormonal regulation of behavior

Sex determination for some time has been known to be under the control of an X-specific gene (German et al., 1978). It appears now that a region of chromosome Xp21 affects sexual differentiation (Bardoni et al., 1994). The mechanisms through which these genes operate are not fully understood, yet work in developmental neurobiology and neuroendocrinology is providing new information about the processes through which gonadal hormones pattern sexual differentiation. Early hypotheses about the action of gonadal hormones on the development of reproductive physiology and behavior, which proposed that hormones in early fetal life produce "organizational," that is, permanent, changes and in postnatal life "activate" sex-specific behaviors have been amended. Current theories hold that steroid hormones effect sexual differentiation by gaining control over certain key maturational processes in the brain by influencing cell proliferation, cell migration, ontogenetic cell death, and synaptogenesis at critical prenatal periods and in postnatal life (MacLusky and Naftolin, 1981; Kelley, 1986).

McEwen's studies (McEwen, 1981) in rats have mapped and identified estrogen-sensitive cells in many brain areas, one example being neurons in ventromedial hypothalamic regions critical for the female rat's sexual receptivity. Based on research in the female spotted hyena, which exhibits malelike genitalia and dominance over males, yet gives birth, Glickman et al. (1992) have proposed that female sexual differentiation may also be influenced by naturally circulating androgens. Many examples of sexual dimorphic neurons or cell groups in different species now exist; most were identified because they regulate conspicuous male evolutionary characteristics, such as bright plumage, frog croaking, and bird song. In some birds, estradiol may establish the capacity for growth in song-control nuclei, whereas dihydrotestosterone may control the number of neurons that innervate syringeal muscle groups for male song. A particularly telling example is the remarkable and seasonally varying differences in the volume of cell groups that innervate muscles controlling song in male canaries and finches (Nottebohm and Arnold, 1976). Structural differences in female and male brains are reviewed in Chapter Four.

Maternal and attachment behavior

Behavioral endocrinology – how hormones affect behavior and are affected by behavior – was an emerging field 20 years ago (Beach, 1975) and is still in its infancy. Nearly all research has been conducted in nonhuman species. The neurochemical determinants that facilitate recognition and bonding in the infant to the mother have not been clarified, although it is known that physical contact and other cues, for example, visual, auditory, and sensory ones, are necessary conduits (Bowlby, 1982). Conversely, the agents and neuronal pathways that promote affiliative and maternal behavior from the parents to the infant are incompletely understood. Early investigations established the permissive and necessary role of the gonadal hormones, estradiol and progesterone, for maternal behavior (Bridges, 1984). It appears now that central neuropeptide pathways are indispensable for some social behaviors and that oxytocin, a cyclic octapeptide secreted by the paraventricular and supraoptic nuclei and stored in the neurohypophysis, is involved in activating maternal behavior in rodents and many other species (Pedersen and Prange Jr., 1987; Insel, 1990).

Based on studies into the neural correlates of pair bond formation in prairie voles, a mammalian species exhibiting monogamy – unlike rats and mice, which do not pair bond – Insel and co-workers (Carter et al., 1992) have reported that oxytocin release follows sexual behavior and leads to strong selective heterosexual social preferences. Because in the prairie vole physical contact, for instance, sharing a nest, outside of sexual activity is a major component of monogamous behavior, it can be used to characterize social preferences. It appears that oxytocin may be critical for social and sexual bond formation in the female prairie vole; by contrast, vasopressin seems to be more important for pair bonding in the male prairie vole and for inducing paternal behavior in the presence of testosterone (Wang and de Vries, 1993). Vasopressin has also been reported to facilitate social recognition and memory in the male rat by Dantzer and co-workers (Dantzer et al., 1988). Social recognition in rats is based on chemosensory cues and is dependent on circulating androgen levels. By using vasopressin antagonists, Bluthé and Dantzer (1990) demonstrated that vasopressin did not mediate social recognition in female rats, which suggests sexually dimorphic processing of social olfactory stimuli and bond formation in these rodents. On a molecular genetic level, Insel and co-workers (Kirkpatrick, Kim, and Insel, 1994) reported by measuring increased *fos* expression that the medial nucleus of the amygdala of the prairie vole was involved in paternal and maternal behavior. Greenberg's group (Brown et al., 1996) has shown in mice that the capacity to react with an immediate postpartum nurturing response to the young is genetically controlled by *fosB*. *FosB* is one of the early immediate genes uniquely activated by environmental stimuli, and its cellular and behavioral effects would complement the hormonal regulation of nurturing behavior.

In humans, oxytocin has long been known to be released during parturition and during suckling to facilitate milk ejection, whereas vasopressin has been reported to promote learning and memory (Kovacs and Telegdy, 1985). During the long period of human gestation, estrogen and progesterone act as priming agents. It is likely, although it has not been established, that oxytocin and vasopressin not only play a role in rodents but also mediate human parental and social behavior (Rosenblatt, 1994).

Somatic growth

Speed of growth is fastest from the beginning of conception to birth and thereafter declines gradually, except during the adolescent growth spurt. Whereas growth in height is fairly steady until adolescence, 80 percent of the postnatal growth of the skull, the brain, the eyes, and the ears is completed by the end of the second or third year of life (Marshall and Tanner, 1969). The size of the head approaches adult size by age 10, but changes in the jaw and other parts of the face and overlying soft tissues are apparent during and after puberty.

The trunk develops earlier than the legs, and the feet are more developed than the calf or thigh. Interestingly, at birth the male forearm is already longer than that of the female, whereas in females, as opposed to males, the second finger is more often longer than the fourth finger. Growth velocity is quite different in lymphoid tissues, which reach "adult" size by age 6, double in size by puberty, and under the influence of sexual hormones shrink back to half this size. Subcutaneous fat thickness increases rapidly in the first through the second year and gradually declines until the age of 6 or 7, when children tend to look thin. From age 8 or 9 onward, fat thickness on the trunk and arms increases until the time of puberty. Prepubertal children of both sexes have the same range of heights and equal body and skeletal mass and body fat; therefore, in childhood girls and boys actually have similar body dimensions.

Constitutional factors: temperament and personality

Chess and Thomas (1968) were the first among developmental psychiatrists to record systematically individual styles in infants and children. These individual behaviors came to be known as temperaments. Behavioral observations in a sample of children who were part of the New York Longitudinal Study, begun in 1956, showed that two fifths of the children displayed an easy temperament, about 10 percent were difficult, and about 15 percent were slow to warm up, with the remainder not clearly belonging to either group. The child's sleep and feeding patterns and the reaction to the environment provided further behavioral constructs – the biologically regular or irregular infant, high or low activity levels, high or low sensory thresholds, high persistence–low distractability, and varying combinations of each. Besides identifying temperamental characteristics, the investigators were interested in helping parents understand their children's individual differences and using this knowledge to respond to and guide their children. Kagan and his group (Kagan, Reznick, and Snidman, 1987) have continued this work on inherited profiles and have focused on a temperamental category called inhibited or uninhibited to the unfamiliar, for example, children who are timid, shy, and inhibited in response to novel stimuli as opposed to children who are affectively spontaneous, sociable, and fearless in new situations. They have shown that in a certain proportion of children these behavioral tendencies are stable and that a relationship exists between behavioral inhibition and biologic indexes such as plasma cortisol levels and heart rate responses, suggesting inherent differences in arousal and reactivity, perhaps influenced by hypothalamic activity. So far, most studies on temperament have not analyzed sex differences.

Environmental factors: sexual and female identity

In any society, a child lives with individuals of all types and ages, classified into female and male, who are conspicuous by their primary sex characteristics. For children, the clearest distinctions are of the two sexes and the role of each sex within the family; hence, femaleness or maleness is a child's first identification (Mead, 1949). Once this identification is made, the child begins to compare and define herself with respect to other characteristics and abilities and to learn how others view and relate to her. If children understand first in the family and in their culture that their sensations, feelings, reactions, and actions are meaningful and effective, they memorize these experiences and integrate them into Children and adults continuously reinterpret their experiences as their minds and bodies mature. In every society girls learn early not only about their bodily differences but how such differences fit into the social organization. If prestige is accorded to women, girls will be more likely to value feminity.

Each female child grows up in her own cultural tradition. Despite marked differences in appearance and temperament, no universal characteristics or behaviors are exclusively associated with either sex across cultures. Divisions of labor are present in any society, not only between the sexes. What counts is whether bearing children is considered not only an activity unique to women but also enough for women, and whether talented and gifted women have access to activities in science or the arts and to public life. As long as women cannot own property or cannot vote – for instance, Swiss women gained suffrage only in 1971 – or are denied the opportunity to train and use their minds, they are likely to suffer a loss in their sense of self.

Puberty and adolescence

Puberty in females

Puberty reflects maturation of the hypothalamic-pituitary-gonadal axis, a process that begins early in fetal life. Hypothalamic luteinizing hormone-releasing hormone (LHRH) neurons originate in the olfactory epithelial placode and from there migrate via the forebrain to the hypothalamus. Primordial follicles appear during the fourth and fifth months of fetal life. Follicular growth occurs during fetal life, and in childhood, yet before puberty, all developed follicles undergo atresia (Grumbach and Kaplan, 1990). In the fetus and at birth estrogen levels are high because of the conversion of fetal and maternal steroids by the placenta. In the newborn, plasma estradiol levels drop precipitously in the first days of life and remain low until puberty. By contrast, plasma levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) rise intermittently to adult values during the first 2 years after birth. Subsequently, LH and FSH levels decline and remain low until puberty (Jakacki et al., 1982). FSH levels rise during the early stages of puberty, and in late prepuberty augmented release of LH during sleep is observed. During puberty, the amplitude and frequency of gonadotropin pulses increase, leading to episodic LH secretion during the day, rising in total over a hundredfold. These events lead eventually to the appearance of secondary sexual characteristics, the adolescent growth spurt, and fertility.

Adolescent growth spurt

On average, girls begin the adolescent growth spurt 1–2 years earlier than boys, and therefore girls are typically taller than boys around age 12. Because girls reach peak height velocity about 1.3 years before menarche, most girls grow no more than 1–7 cm after menarche. Menarche usually occurs as growth in height is slowing down. The hormonal mechanisms involved in growth at puberty are not well understood. Estrogens may stimulate growth by increasing production of insulin-like growth factor-1 (IGF-1). Prolonged delay of puberty can prolong growth in stature, but only under conditions of good nutrition and normal activity levels. If delayed puberty is due to low body fat and excessive exercise, prepubertal growth is not assured, but catch-up growth has been reported with weight recovery (Prader, Tanner, and von Harnack, 1963). During puberty, boys in contrast to girls lose fat on limbs and on the trunk, and they usually become leaner, whereas girls on average accumulate nearly twice as much body fat as boys. Shape differences are produced by the widening of boys' shoulders and the enlargement of girls' hips. Ultimately, boys have more muscle mass, larger bones, and therefore higher bone-density measurements than girls. Skeletal maturation can be assessed by comparing radiographs of the hand, the knee, or the elbow with standards of maturation in a reference normal population. Bone age, an index of ossification and epiphyseal fusion, is useful for predicting the age of menarche. In delayed puberty, bone age correlates better with the appearance of secondary sexual characteristics than with chronologic age.

Skeletal growth is not complete by the end of adolescence because the vertebral column can continue to grow until about age 30. Tanner's growth charts (Tanner, Whitehouse, and Marshall, 1975) from longitudinal and cross-sectional data of British children have been updated and estimated for populations in other countries – in the United States by the National Center for Health Statistics (Hamill et al., 1979). Surveys of workers and military recruits indicate that the average age for attaining adult height was much later in past centuries (Tanner, 1981). Better nutrition and improved health in childhood and adolescence largely explain the earlier growth and the growth acceleration in U.S. and West European young adults. Fogel (1993) has calculated that around 1855 about two thirds of young adult males in Holland, a country with a fairly genetically homogeneous population, were below 5 feet 4 inches (168 cm), whereas in 1980 a mere 2 percent of males remained below this height. There is clear evidence that emotional factors affect growth; for instance, emotional dwarfism is a well-described phenomenon in childhood (Powell, Brasel, and Blizzard, 1967), and Pine, Cohen, and Brook (1996) have reported from a prospective epidemiologic study that anxiety disorders in childhood appear to predict relatively short stature in young adulthood in females, but not in males.

Endocrinology of puberty

The episodic FSH and LH secretion that occurs during early puberty, mainly at night, gradually increases in amplitude and frequency, and by late puberty daytime secretory peaks reach a plateau (Reiter et al., 1987). Amplified FSH pulses lead to secretion of estradiol from the ovary. About 10 percent of circulating estradiol arises from extraglandular conversion of testosterone and androstendione (Grumbach and Kaplan, 1990). Plasma estradiol concentrations rise steadily through the stages of puberty until they reach mean levels of 50 pg/ml in the follicular phase, 220 pg/ml at midcycle, and 150 pg/ml in the luteal phase at maturity. Anovulatory cycles are common in the first year after menarche (Apper and Vikho, 1977). Estradiol and testosterone are highly (95–97 percent), yet reversibly, bound to sex steroid–binding globulin (SBG) present in equal levels in boys and girls during prepuberty. SBG decreases with puberty in girls less than in boys (Lindstedt et al., 1985). Beginning at age 8, there is an increase in adrenal steroids, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) – a phenomenon called adrenarche – which continues through ages 13 to 15 years. The circadian rhythm of DHEA release parallels the diurnal rhythm of cortisol secretion.

Secondary sex characteristics

Puberty for girls is unmistakable and dramatic, whereas for boys the events unfold slowly. In the majority of U.S. girls (95 percent) the first signs of puberty, either breast or pubic hair growth, appear between the ages of 8 and 13 years (mean 10.5 years) (Fig. 1.1) (Marshall and Tanner, 1969). Actually, increase in

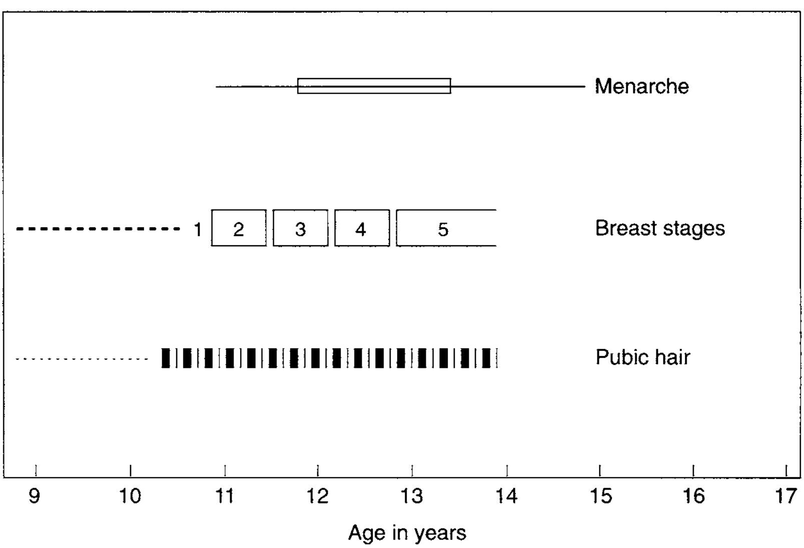

Figure 1.1. Sequence of pubertal changes in females.

height velocity rather than breast development may be the first sign of puberty in girls. The development of the breast is primarily under the control of estrogens secreted by the ovaries, whereas growth of pubic and axillary hair is mainly under the influence of androgens secreted by the adrenal gland and the ovary (Drife, 1986). Axillary hair appears at approximately age 13 in U.S. girls. Breast development may be asymmetrical for several months and may cause unfounded concerns for the girl and the parents. Marshall and Tanner (1969) have provided the most widely used classification of the stages of breast development, based on specific characteristics common to the female breast:

Stage 1: elevation of papilla only.
Stage 2: breast bud stage.
Stage 3: elevation of breast and papilla as a small mound, enlargement of the areola.
Stage 4: projection of areola and papilla from a secondary mound above the level of the breast.
Stage 5: mature stage, recession of areola to the general contour of the breast.

The stage of breast development usually corresponds to the stage of pubic hair development.

Menarche

Historical documents provide evidence that in industrialized countries puberty now occurs much earlier (Largo and Prader, 1983). The average age of menarche has decreased by about 2–3 months per decade for the past 150 years, from ages 17–18 to about 12–13 years. The average age at menarche is now 12.8 years (Wyshak and Frisch, 1982). This maturational advancement is, like the growth acceleration, largely the result of improved nutrition and health and better socioeconomic conditions. In point of fact, moderate obesity up to 30 percent above normal weight is associated with earlier menarche, whereas pathologic obesity leads to delayed puberty (Hartz, Barboriak, and Wong, 1979). Under optimal conditions of nutrition and child care, genetic factors largely determine the onset of puberty (Zacharias, Rand, and Wurtman, 1976).

An interesting phenomenon that was first documented by McClintock (1971) and contested by Wilson (1992), the convergence of menstrual onset dates, or menstrual synchrony, among girls and women who are friends or living together is still not well understood. Recent work by Weller (Weller, Weller, and Avinir, 1995) suggests that the critical factor may not be the physical contact through close living conditions but emotional synchronization through close friendships and intensive social contact.

Psychological growth

Adolescence is a time of intense emotional experiences, and sometimes eccentric behavior, but not necessarily a time of turmoil (Offer, Ostrov, and Howard, 1981). Larson and co-workers (Larson, Csikszentmihalyi, and Graef, 1980) found that adolescents of both sexes, who were paged throughout the day at random intervals and requested to record their mood, reported more rapid and more marked positive and negative mood swings than adults. Continuous turmoil might actually be a sign of psychopathology. Masterson Jr. (1968) observed that many of the tumultuous teenagers displayed symptoms of an affective disorder by late adolescence. Relationships between plasma concentrations of sexual hormones and depression, aggression, or happiness in adolescence are weak and inconsistent (Buchanan, Eccles, and Becker, 1992). So far, it has been difficult to determine even how influences of plasma estrogens or androgens are transmitted to the brain to produce mood changes, because in the male testosterone is extensively converted to estradiol and in smaller amounts to dihydrotestosterone in the brain. Very likely, estrogen receptors also modulate brain neurons in the male (McEwen, 1981).

Preexisting depression has been reported to be more strongly related to depression than coexisting plasma estrogen values (Susman, Dorn, and Chrousos, 1991). Several studies have shown that adolescent girls more frequently report depressed mood and anxiety than adolescent boys (Kandel and Davies, 1982; Petersen, Sarigiani, and Kennedy, 1991; Casper, Belanoff, and Offer, 1996), although no relationship between mood and pubertal status has been observed. One hypothesis that has undergone testing is that girls become oversocialized. Girls tend to be more concerned with expectations and moral issues, to depend more on external approval, and in consequence to develop more easily a negative self-image (Gjerde and Block, 1991). In most cultures, girls are socialized into inhibiting the expression of anger in adverse situations and into internalizing their feelings. Other factors that may account for the higher incidence of depression in women are discussed in Chapter Four.

Body and self-image

Body image in our appearance-conscious society has become a fashionable topic of conversation, mistakenly assumed to reflect a morbid preoccupation with an ideal body shape. Indeed, fear of fatness and of being overweight were expressed by 30 percent of 9-year-old girls in California (Casper, 1995a). Such expression of body dissatisfaction in the young has become a source of concern for parents and teachers. In girls, the preoccupation with weight seems to increase with increasing age, whereas boys tend to interpret weight gain as a sign of strength (Richards, Casper, and Larson, 1990). Studies on the body image in relation to the timing of the onset of puberty have consistently found that in girls early pubertal development is associated with a negative body and self-image (Gargiulo et al., 1987), whereas in boys early puberty affects the body image positively. Early-maturing girls report more conflict with their parents and have been found to describe more depressed affect in 12th grade than late-maturing girls (Petersen, Sarigiani, and Kennedy, 1991). The fact that early maturers are generally shorter than late maturers, but usually weigh more (Garn et al., 1986), might contribute to the negative effects of early menarche, defined as menarche before age 11.

Body image is actually a neutral term (Schilder, 1935). It indicates simply that the brain retains a schematic representation of the body, which under normal conditions rarely, if ever, reaches awareness. For instance, the transformation of the child's into a woman's body, although it occurs gradually, brings with it dramatic changes, yet most of the time these pubertal changes are integrated smoothly into the body image and comfortably accepted into the self-concept. Similarly, most women adapt easily to the changed bodily contours of pregnancy.

Self-concept and self-esteem

Self-esteem, defined in Webster's dictionary as "holding a good opinion of oneself and one of self-respect," develops early in life. Self-regard forms part of the self-concept and draws its substance from the individual's physical and psychological attributes – from the person's genetic disposition, temperament, personality, intelligence, special talents, and attractiveness – and not least from environmental influences. In classical analytic theory the infant moves from being the center of attention and from a position of control (primary narcissism) to the realization of his or her limits and dependence on others (Freud, 1914). The infant learns that despite unavoidable frustrations inherent in any relationship, he or she will be cared for and loved. Such early aquired confident expectations underlie the concept of basic trust (Erikson, 1963). Under optimal conditions, a certain amount of neglect and disappointment leading to anxiety and angry protest will be expected and processed without shattering the individual's sense of worth and confidence.

Most subsequent theories have elaborated on these early relational foundations of self-esteem and their implications for separation and individuation (Mahler, 1963). In a recent study (Roy, Neale, and Kendler, 1995) based on the

Virginia Twin Registry that asked monozygotic and dizygotic twins to complete the Rosenberg self-esteem questionnaire, individual experiences were found to account for about half of the variance contributing to self-esteem. The other half was found to be inherited, with neuroticism and depression contributing most to heritability. Self-esteem was also noted to be fairly stable. Over and above self-esteem, family norms, societal and cultural codes, and the girl's own expectations and conscience subtly mold and negotiate the self-concept in childhood and adolescence and throughout adult life.

Adolescence is a time of increased self-evaluation and at the same time of internal disengagement from family values. Self-consciousness increases with exposure to peer group and societal values as the adolescent begins to realize that social roles and social positions in adult life are fundamental sources of identity. Comparisons and competition create continous conflicts that can affirm or threaten the self-image and self-concept. For girls who grew up in a healthy family and who were accustomed to a matrix of relationships outside the family, autonomy will include reliance on others, whereas for girls who grew up in emotional isolation in dysfunctional families, independence might come to connote self-sufficiency. If female adolescents have been raised with, and as a consequence have developed, an ideal of perfection, there is a constant threat of failure. If their ideal has grown out of a realistic assessment of their innate abilities, their expectations and performance will be in tune with their abilities, and their activities will increase their self-confidence.

Female adolescents for the most part are and feel physically healthy (Casper, Belanoff, and Offer, 1996), but adolescence is a time when minor psychiatric morbidity and more serious disorders rise in frequency, with many of these disturbances showing a female preponderance. Anorexia nervosa typically has its onset in early adolescence, and bulimia nervosa is observed in the late teens (see Chapter Seven). More dramatic is the increased incidence of affective disorders and anxiety disorders and the rise in attempted suicides. Even though only 15–20 percent of female adolescents may be affected (Graham and Rutter, 1973; Leslie, 1974; Hawton and Goldacre, 1982; Angold and Costello, 1995), it is important to recognize these disturbances so that treatment can be initiated.

Conclusions

In industrialized countries, and increasingly all over the world, female adolescents grow up better educated and with more freedom and more choices than their grandmothers had, even if the independent woman may still be considered a contradiction in terms. Greater opportunities, as diverse as they might be, entail greater aspirations and efforts and more responsibilities. It remains a fact of life that women alone can bear children. The debate about how women who are fulfilling several roles will fare in this changing environment has led to many investigations. To give one example, Elliot and Huppert (1991), who surveyed a large British sample of married women under the age of 45, observed that paid employment, particularly full-time work, was beneficial for middle-class women but detrimental for working-class women. Women with one or more preschool children showed the highest prevalence of psychiatric symptoms; surprisingly, the study observed no association between mental health and social class. Women's greater readiness for symptom recognition (Kessler, Brown, and Boman, 1981) might be fortuitous and protective in times of limited access to health care, and so might be the increase in the number of female physicians, who have been found to be more attuned to preventive care for women than male physicians (Lurie et al., 1993). Health and disease are multifaceted. The chapters in this volume describe factors contributing to the disorders for which women are uniquely at risk and present evidence for hormonal and environmental influences on women's health. The last two chapters consider issues in psychopharmacology pertinent to women and present an overview of ongoing intervention trials with a hormonal or a behavioral component in female populations. We hope that greater awareness of the close connections among social, psychological, endocrine, and constitutional factors in disease states will improve treatment options and raise fresh hypotheses for research in women and in men.